No Association between D_2 Dopamine Receptor (DRD2) "A" System Alleles, or DRD2 Haplotypes, and Posttraumatic Stress Disorder

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Background: *Association studies between marker alleles at the D_2 dopamine receptor gene (DRD2) and various psychiatric illnesses have produced conflicting results. Reports of allelic associations were originally made with alcoholism, but were then extended to other psychiatric disorders, including posttraumatic stress disorder (PTSD).*

Methods: *We studied allele frequency of the DRD2 TaqI "A," "B," and "D" system markers in 52 European-American subjects with diagnoses of PTSD (based on structured interviews).*

Results: *Frequency of the A1 allele in this sample was .15, not significantly different from the .19 allele frequency seen in 87 control subjects. We were thus unable to replicate the previous reports of allelic association between the DRD2 TaqI "A1" allele and PTSD. There were also no significant differences in allele frequency for the "B" or "D" systems. We then computed three marker (TaqI "A," "B," and "D" system) haplotypes for the sample; DRD2 haplotype frequencies also did not differ between control subjects and subjects with PTSD.*

Conclusions: *We conclude that DRD2 alleles are not associated with PTSD in this sample, and that genetic variation at the DRD2 locus is not likely to be an important contributor to risk for this disorder.* Biol Psychiatry 1999;45:620–625 © *1999 Society of Biological Psychiatry*

Key Words: Posttraumatic stress disorder, genetic association, D_2 dopamine receptor, TaqI "A" system, candidate genes, haplotypes

Introduction

Many association studies between psychiatric phenotypes and alleles at the D_2 dopamine receptor locus (DRD2), principally considering the TaqI "A" system, have been completed, but whether or not any valid association with a physiological basis has been demonstrated remains controversial. Blum et al (1990) first proposed an association between the DRD2 TaqI A1 allele and alcoholism in 1990. Since then there have been many subsequent research reports, reviews, and meta-analyses (e.g., Gelernter et al 1993; Uhl et al 1993). Blum et al (1997) have postulated the existence of a "reward deficiency" syndrome related to polymorphic variation at the DRD2 locus.

Twin study data suggest that posttraumatic stress disorder (PTSD) has a heritable component, with genetic factors accounting for roughly 13–34% of the variance for specific symptom clusters (True et al 1993), and that genetic factors may influence exposure to trauma (Lyons et al 1993). Family history data (Davidson et al 1989) support a genetic relationship between PTSD and other anxiety disorders. The demonstration of genetic factors relating to risk for PTSD suggests that eventually, genes influencing risk for this disorder may be identified.

Acute and chronic stress both affect central dopamine systems; dopaminergic innervation of the prefrontal cortex is highly sensitive to stress (Thierry et al 1976; Deutch and Roth 1990). It has been hypothesized that patients with PTSD suffer from a functional deficit in dopaminergic tone that compromises their ability to develop effective coping strategies for dealing with trauma (Deutch and Young 1995). Further, it has been proposed that such a deficit might contribute to hypervigilance, paranoia, and greater susceptibility to trauma-related contextual stimuli.

Empirical studies of dopamine in humans with PTSD have been limited and inconclusive. Increased levels of 24-hour urine dopamine excretion have been reported in combat veterans with chronic PTSD (Yehuda et al 1992) and in women with sexual abuse-related PTSD (Lemieux

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Received November 5, 1997; revised February 3, 1998; accepted February 13, 1998.

0006-3223/99/$19.00
PII S0006-3223(98)00087-0

and Coe 1995). Additionally, in two separate studies, higher levels of 24-hour urine homovanillic acid have been found in sexually abused girls than in controls (Debellis et al 1994; Putnam and Trickett 1997). Finally, plasma dopamine has been reported as elevated in a small cohort of combat veterans compared to controls (Hamner and Diamond 1993). Dopamine system genes are therefore reasonable, but not compelling, candidates for influencing risk for PTSD.

This possibility was first investigated by Comings et al; they first reported a significant association of DRD2 TaqI "A1" (DRD2*A1) alleles with PTSD in 1991 (Comings et al 1991). In that sample of 35 European-American (EA) PTSD patients, DRD2*A1 allele frequency was .26 and "carrier" (i.e., DRD2*A1 homozygotes plus heterozygotes) frequency was .46. All of these subjects were also diagnosed with drug or alcohol abuse.

Comings et al (1996) also reported a genetic association between the DRD2*A1 allele and PTSD in a sample of 37 subjects. This study was framed as a comparison of combat-exposed subjects with or without PTSD on an addiction treatment unit. All subjects were EAs who were alcohol or drug dependent. All comparisons made were between "A1" "carriers" (i.e., A1A1 plus A1A2 subjects) and "A2" homozygotes; neither allele frequencies nor genotypes were reported, limiting possible comparisons between that study and other studies, including the present one. Comings et al (1996) speculate that "severe combat may act as a 'stress test' for those with the D_2A1 allele" (p 371). The "initial" sample included 24 subjects with PTSD and 8 subjects without PTSD; the "replication" study included 13 subjects with PTSD and 11 subjects without PTSD. Overall, 59% of the 37 subjects with PTSD were "A1" carriers, compared to 5% of the 19 non-PTSD subjects ($p = .0001$). The design of the study, which allowed for a comparison of subjects with or without PTSD but all of whom were combat-exposed, was well-conceived because, if the hypotheses were correct and the DRD2*A1 allele were associated with PTSD, the group with the environmental exposure but without PTSD would be expected to be depleted of DRD2*A1 alleles, facilitating demonstration of an association; however, this strategy also resulted in use of a rather small comparison group, a total of 19 subjects. The small sample size for this study limits the conclusions that may be drawn from it, despite the highly significant finding.

In an attempt to replicate the Comings et al (1991, 1996) findings, we studied DRD2 TaqI "A" system allele frequencies in a sample of 52 EA subjects with diagnosis of PTSD. We found DRD2*A1 allele frequency and haplotype frequency similar to that in our previously reported control group (Gelernter et al in press), and were thus unable to replicate the findings of Comings et al (1991, 1996).

Methods and Materials

Clinical Methods

All subjects with PTSD were EA Vietnam combat veterans being treated in the Posttraumatic Stress Disorder Program of the VA CT Healthcare System, West Haven, which is also the Clinical Neurosciences Division of the National Center for PTSD. Consensus diagnoses were made on the basis of structured clinical interviews [SCID (Spitzer et al 1992) or SADS-L (Spitzer and Endicott 1975)] and clinical evaluations by psychologists and psychiatrists specializing in PTSD. Of the 52 subjects, 8 were interviewed using the SADS, and 44 using the SCID (some by PTSD module only). Mean age was 44.6 ± 3.6 (SD) years. The majority of the PTSD subjects were taking part in other research studies; some, however, were assessed after presenting for clinical treatment.

Comorbidity data were available for 41 subjects (79%). Of those subjects, 38 (93%) had diagnoses of either alcohol or substance dependence, or both (alcohol dependence, 31; substance dependence, 25). Of the 3 subjects who met criteria for neither alcohol nor substance dependence, 2 had alcohol abuse, and 1 of these had substance abuse as well.

There were 87 EA control subjects. Sixty-six (76%) of these were screened to exclude alcohol or drug dependence; 43 were screened by SCID or C-DIS-R and 23 by nonstructured interview. Of the screened subjects, there were 4 with history of mood disorders among the EAs; otherwise there were no Axis I diagnoses. Most of the control subjects were participating in other research studies. We have previously demonstrated that including unscreened controls is not expected to significantly reduce power except for a very common phenotype (Gelernter et al 1991). DRD2 allele and haplotype frequencies in this same control group have been reported previously (Gelernter et al in press).

LABORATORY METHODS. DNA was extracted from whole blood by standard methods. We used polymerase chain reaction-formatted restriction fragment length polymorphism methods for the DRD2 TaqI "A" (Grandy et al 1993; GDB accession: 250184), "B" (Castiglione et al 1995), and "D" (Kidd et al 1996) polymorphic systems.

DATA ANALYSIS. For comparison of DRD2 allele frequency by diagnosis within populations, 2×2 χ^2 was used. To evaluate deviation from Hardy–Weinberg expectations, we used a simulation approach due to the small number of A1 homozygotes observed, with the HWSim program and 1000 simulations (Cubells et al 1997).

HAPLOTYPE ANALYSIS. Haplotype analysis was accomplished using the 3LOCUS program (Long et al 1995), which computes estimated haplotype frequencies using an expectation maximization (E-M) algorithm. This program also computes pairwise and three-way disequilibria. The statistical significance of the G test statistic comparing the full three-locus disequilibrium model (all pairwise disequilibria plus three-way disequilibria) (M8) with the null hypothesis of no

disequilibrium (M0) was evaluated empirically by comparison with a simulated null distribution using 10,000 replications (Long et al 1995).

Estimated haplotype frequencies were then compared using the CLUMP program (Sham and Curtis 1995). A standard 2 × 5 χ^2 ("T1") was computed, and its statistical significance determined empirically using 1000 simulations.

Results

DRD2*A1 allele frequency [f(A1)] in the PTSD subjects was 0.15. Genotype distribution was A1A1 (1 subject), A1A2 (14), and A2A2 (37); thus the A1 "carrier" frequency was .29. This is not a significant deviation from Hardy–Weinberg expectations (HWE) (p = 1).

For our previously reported control group, f(A1) = .19, which does not differ significantly from the PTSD sample (2 × 2 χ^2 = 0.35, p = .55). The nonsignificant difference is in the opposite direction of the significant difference observed by Comings et al (1991, 1996). Genotype distribution was A1A1 (2 subjects), A1A2 (29), and A2A2 (56); the A1 "carrier" frequency was .36. As for the PTSD subjects, this is not a significant deviation from HWE (p = .55). Analysis by carriers rather than alleles again shows no difference between the PTSD group and the control group (2 × 2 χ^2 = 0.41, p = .52), and the nonsignificant difference is, again, in the opposite direction of the significant difference observed by Comings et al (1991, 1996). We also did not observe significant differences in allele frequency for the "B" system (2 × 2 χ^2 = 0.41, p = .52) or the "D" system (2 × 2 χ^2 = .21, p = .65).

Allele frequencies for all three systems are presented in Table 1. A total of only four haplotypes was observed in the PTSD subjects (A1-B1-D2, A1-B2-D1, A2-B2-D1, and A2-B2-D2). Estimated haplotype frequencies did not differ between the PTSD subjects and European-American controls (T1 χ^2 = 2.27; $p \sim .735$; ns) and appear closely similar (Figure 1). There was highly significant linkage disequilibrium across these three polymorphic systems in the PTSD subjects (G = 66.08; $p < .0001$).

Table 1. Allele Frequencies for Three Polymorphic DRD2 Systems

	Control ($2n$ = 174)	PTSD ($2n$ = 104)
f(A1)	.190	.154
f(B1)	.161	.125
f(D1)	.609	.644

European-American controls, from Gelernter et al (in press).

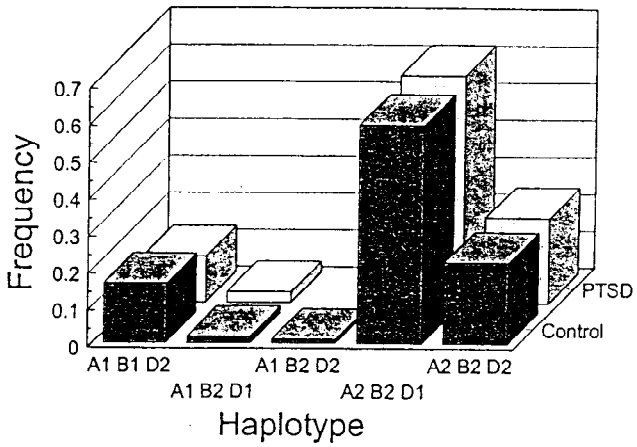

Figure 1. Estimated haplotype frequencies including three polymorphic DRD2 systems (European-American controls, from Gelernter et al in press).

Discussion

Our data do not support an allelic association between DRD2 TaqI "A" system alleles and PTSD, and thus we were unable to confirm the findings of Comings et al (1991, 1996). We also studied haplotype frequencies including data from three polymorphic DRD2 loci, the "A," "B," and "D" systems, which should have increased our potential to detect an association with a particular haplotype potentially in linkage disequilibrium with PTSD; however, we did not find any difference in haplotype frequency between our PTSD and control subjects. The linkage disequilibrium across this locus is seen most clearly between the "A" and "B" systems, where all B1 alleles were observed on A1 chromosomes, but note also that, although the D1 allele is more common than the D2 allele among both controls and PTSD subjects, all A1-B1 chromosomes observed in the present study were also D2.

Most of the PTSD subjects had comorbid alcohol or substance dependence, or both; the lack of increased DRD2 Taq I "A1" or "B1" allele frequency in a largely substance-dependent group is consistent with our previous data (e.g., Gelernter et al 1991, in press), although other authors have reported increased frequencies of those alleles in similar samples (see, e.g., review by Uhl et al 1993).

The largest difference in the phenotypes measured (PTSD in this case) should be seen in a comparison of opposite homozygotes, regardless of whether the polymorphism assessed is directly responsible for the phenotypic effect or if it is a marker for it. Comings et al (1996) used "carrier prevalence" rather than allele frequency for their comparisons, in effect counting homozygotes for the allele of interest with the same weight for analysis as heterozygotes; however, using "prevalence" as an abbreviated way

to refer to allele distribution in a population (and equating "carriers" of a rare, presumably disease-influencing allele, with homozygotes for it) makes sense only for a completely dominant disease (like Huntington's disease), and only then if the polymorphism studied is the disease mutation itself or a marker in *complete* linkage disequilibrium with the disease mutation—relatively unlikely circumstance. Whether or not the disease is completely dominant, when dealing with a linked marker in incomplete linkage disequilibrium with a disease-influencing mutation, homozygotes for the marker should differ phenotypically from heterozygotes across a population, because they are more likely to carry chromosomes with the disease-influencing mutation than heterozygotes. To illustrate this point, consider a marker allele with 80% predictive value for presence of a disease-influencing mutation. Heterozygotes for the marker allele then have an 80% chance of carrying at least one disease-associated chromosome, but homozygotes have a 96% chance [$1-(0.2^2)$]. Thus, even for a completely dominant disease, homozygotes for a marker allele are more likely to carry a disease-associated allele than heterozygotes, and the two forms of "carrier" are not identical. (Nevertheless, when a gene that actually has a dominant effect is studied, "carrier" rather than allele frequency comparisons would be expected to increase statistical power.)

Use of only screened controls has been advocated by some authors for studies of DRD2 allele frequencies or otherwise suggested to be an important issue (e.g., Cloninger 1991; Turner et al 1997), but it has also been demonstrated that use of screened controls might provide only limited increases in power to detect associations, with small increases in power for a disorder as common as alcohol dependence, with a prevalence of 13% (Gelernter et al 1991). PTSD has a lower prevalence, estimated at 7.8% (Kessler et al 1995). Moreover, when screened control samples are used, the goal is often to exclude as many subjects with any psychiatric diagnosis as possible. This could potentially introduce artifact in several ways. For example, suppose the phenotype under study is phenotype P and a different phenotype, Q, may either be comorbid with P or exist independently. Suppose further that Q is really associated with the candidate allele under study but P is not. Then if the control sample is cleansed of both phenotypes P and Q, but the affected sample contains significant numbers of individuals with comorbid P and Q, an association may be detected (with a large enough sample) with Q but be attributed to P. If the subjects with phenotype Q are not excluded from the control sample, an incorrect conclusion is less likely. Thus, choosing the most appropriate composition of a control sample is a complex issue, and under many circumstances an unscreened (random population) sample is theoretically preferable to a screened sample, because it may provide a better approximation of the ideal comparison group, that is, one that differs from the affected group for no characteristic other than affection with phenotype P. Since comorbidity with PTSD is very high (estimated at 88% for men and 79% for women in a large sample; Kessler et al 1995), this issue has particular relevance for genetic association studies of PTSD. Ninety-three percent of our subjects for whom comorbidity data were available also had diagnoses of alcohol or substance dependence.

Existence of functional correlates for the DRD2 polymorphisms also remains controversial. Mutation analysis studies of the DRD2 gene have so far failed to demonstrate existence of a coding sequence polymorphism common enough to provide a physiological basis for an association (e.g., Sarkar et al 1991; Seeman et al 1993; Gejman et al 1994). If these studies are correct, the only way to account for such an effect is by hypothesizing a mutation outside of the coding region, which might act by an effect on regulation of the gene [resulting, e.g., in altered numbers of D_2 receptors in brain, as supported by the postmortem study of Noble et al (1991)] or stability of the messenger RNA. If an effect of DRD2 alleles on D_2 receptor B_{max} could be demonstrated in vivo, this could be explained by a noncoding region polymorphism, and would provide a physiological explanation for the positive association findings. The recent report by Arinami et al (1997) of a polymorphism in the DRD2 promoter with preliminary evidence for a functional effect supports this view; however, we (Laruelle et al in press) evaluated the hypothesis of an effect of DRD2 alleles on D_2 dopamine receptor binding potential directly in living subjects using a single photon emission computed tomography paradigm, and failed to find support for an association.

Thus, the present results do not confirm that genetic variation at the DRD2 locus influences risk for PTSD. Power analysis based on the figures reported by Comings et al (1996) suggested that a sample size of 28 subjects (i.e., 14 in each group) should have been sufficient to detect an effect with $\alpha = .05$ and 95% power (one tailed) (Brent et al 1993). This estimate is complicated by the fact that this analysis presumes use of combat controls, which were used by Comings et al (1996) but not by us, so the sample size actually required should be presumed to be somewhat larger. Even taking this factor into account, our sample size of 52 subjects and 87 controls exceeds these figures to such a great extent that it seems reasonable to state that our sample had sufficient power to detect an effect of the size shown by Comings et al (1996). Future study could resolve this issue either through use of

considerably larger patient samples or, preferably, through use of family controlled association designs.

The work was supported in part by funds from the U.S. Department of Veterans Affairs [USVA National Centers for PTSD and Schizophrenia Research, the VA–Yale Alcoholism Research Center, and the VA Medical Research Program (Merit Review grant)], and NIMH grants MH01387 and MH30929.

The authors wish to thank Ann Marie Wantroba and Harold Landis (technical assistance) and Kathleen Bonvicini (data management).

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